Opinion

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NOW vs LATER brain circuits: implications for obesity and addiction

Nora D. Volkow and Ruben D. Baler

National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD 20892, USA

Balancing behaviors that provide a reward NOW versus behaviors that provide an advantage LATER is critical for survival. We propose a model in which dopamine (DA) can favor NOW processes through phasic signaling in reward circuits or LATER processes through tonic signaling in control circuits. At the same time, through its modulation of the orbitofrontal cortex, which processes salience attribution, DA also enables shifting from NOW to LATER, while its modulation of the insula, which processes interoceptive information, influences the probability of selecting NOW vs LATER actions on the basis of an individual's physiological state. Disruptions along these circuits contribute to diverse pathologies, including obesity and addiction.

Delayed gratification: a basic feature of self-control

How do we decide when to do a behavior now versus leaving it for later? Such decisions are influenced by the context, the nature of the behavior, and the probability of its occurrence. For behaviors that have a reward outcome, a premium will be applied to choosing it 'now', whereas for behaviors that have an aversive outcome or that involve exerting effort, the 'later' option will tend to be more appealing. The evolutionarily optimized balance in NOW vs LATER behavioral choices increases the chances of fulfilling immediate needs as well as those that are better served by behaviors designed to attain longer-term goals. Delay discounting (DD) (see Glossary) is an algorithm that quantifies an individual's propensity toward seeking immediate rewards or avoiding aversive commodities, even if later rewarding ones are larger or immediate aversive ones are smaller. To be certain, there are several forms of 'discounting', such as those based on probability [1], and a discount is also applied as a function of how much cognitive or physical effort will be demanded by alternative rewards [2]. However, we focus here on DD because it displays significant test validity, with adverse changes having been associated with several unhealthy behaviors and markers of health status [3], including prepotent responses [4], maladaptive lifestyle choices [5], and a range of psychiatric disorders, including addiction [6–10]. Many factors contribute to or can influence DD rates, including the context, prior experience with the stimulus, physiological states, choice presentation, and previously conditioned responses. The DD literature is vast and fascinating and many of these factors have been extensively described in prior reviews [11–13].

The neurobiology of NOW vs LATER

Decisions involving intertemporal, sustained-effort, probabilistic, and risk-aversion choices rely on overlapping circuits. While much of the neuroanatomical and neurophysiological details that distinguish one function from another remains to be elucidated, it is clear that they are all strongly dependent on DA signaling [14]. Here we focus almost exclusively on the NOW vs LATER (or intertemporal) decision paradigm as it relates to reward choice since this is the aspect that has been most thoroughly investigated. Similarly, the regulatory influence of neurotransmitter systems other than DA on the various components of impulsivity that contribute to DD [15], including lack of premeditation (failure to reflect on consequences), lack of perseverance (inability to remain focused on a task that requires energy expenditure or is distressful), urgency (tendency to act on strong impulses), and sensation seeking (tendency to seek novel and exciting activities) [16], have been reported in the literature [17–21] and are outside the scope of this opinion article.

NOW vs LATER processes are differentially modulated by DA: LATER processes require steady DA signaling in striatal and prefrontal regions to sustain effort as achieved by tonic DA firing, whereas NOW processes are predominantly driven by fast, sharp bursts of DA as achieved by phasic DA firing that drive attention to the salient stimulus. In humans, brain imaging studies have revealed that stimuli that result in fast DA increases in ventral and dorsal striatal regions are experienced as rewarding and generate the desire to attain the stimulus [22] whereas stimuli that trigger slow and steady DA increases do not [23,24]. By contrast, steady DA increases are associated with increases in the ability to exert sustained (i.e., cognitive) effort and to experience the task or stimulus as motivating and interesting [25]. Moreover, these results

Glossary

Delay or intertemporal discounting (DD): the devaluing of a reward as a function of the delay of its delivery.
Effort discounting: the devaluing of a reward as a function of the effort demanded to achieve it.
Probabilistic discounting: the devaluing of a reward as a function of the chances that the reward has of materializing.

Corresponding author: Volkow, N.D. (nvolkow@nida.nih.gov).
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also seem to ascribe a differential role of DA signaling within striatal subregions, the caudate being implicated in inhibitory control of cognitive operations, the ventral striatum (VS) in reward and impulsive choices [26,27], and the putamen in habits and routines [28]. Similarly, within the prefrontal cortex (PFC) the dorsolateral PFC (dlPFC) is associated with improved sustainability of effort [29,30] whereas activity in the ventral PFC (vPFC) is more consistent with temporal discounting of subjective value, and preferentially so in impulsive individuals [31], a differential role consistent with the predominance of their striatal projections from the caudate and the VS, respectively [32].

Additionally, neuroimaging evidence supports the existence of dynamic communication between cortical (including but not limited to the PFC) and basal ganglia regions (including but not limited to the striatum) whenever there is a need to make 'NOW vs LATER' decisions, a system that carries valuation signals not only for appetitive or gain-related stimuli but also for aversive stimuli and for invested effort [33], including responses to economic conflict, moral dilemma, physical pain, and visceral (e.g., moral) disgust [34].

According to a widely accepted model, one of these systems hinges on the preferential activation of high-level deliberative/cognitive processes [e.g., dlPFC, dorsal anterior cingulate cortex (dACC), posterior parietal cortical (PPC) areas] [35] to assess the subjective value of future outcomes and allow people to contemplate or simulate their consequences [36,37]. The second system, which revolves around limbic and paralimbic cortical structures [e.g., ventromedial PFC (vmPFC), VS, hippocampus, amygdala, insula] helps integrate complex appetitive and aversive predictions to coordinate behavior [38] and weigh in whenever there is an opportunity for instant gratification. However, a more holistic model has also been proposed according to which the system as a whole calculates (discounts) the saliency value of a given reward as a function of how soon it will become available [39].

Whatever neurocomputational model of DD turns out to provide the best account of its complex outputs, there is consensus that DA modulates how timing is incorporated into the value of a reward [40]. Indeed, the prediction error signal conveyed by DA neurons includes the predicted time for the reward to materialize. There is also universal consensus that the PFC and striatum [including the nucleus accumbens (NAc)] play crucial roles in cost/benefit analyses of the kinds that underlie NOW vs LATER decisions. In these regions, stimuli and events that induce or predict reward, as well as unexpected or omitted rewards, can trigger rapid changes of DA neuron activity at subsecond to second timescales [41,42]. The modulation of phasic DA firing is regulated by several afferents, of which the most prominent are glutamatergic projections from the PFC, thalamus, amygdala, ventral hippocampus, and brainstem [43–45].

Researchers have uncovered important details about how the PFC and NAc influence DD. In the prelimbic medial PFC (mPFC), DA changes (measured with microdialysis) facilitate shifts in choice bias (important for cognitive flexibility) by conveying information about reward availability, whereas DA changes in the NAc convey information about the magnitude and relative value of a reward in a way that biases choice toward larger, uncertain rewards [46]. Overall, studies indicate that lower DA levels in the PFC contribute to steeper discounting of future rewards by impairing corticostriatal function [47,48]. For example, higher DD rates are observed not only when the executive attention control network [dlPFC, dorsomedial PFC (dmPFC), inferior parietal cortex, cingulate ACC, and precuneus] was less engaged but also when the 'bottom-up' reward valuation network (including the amygdala, hippocampus, insula, and vmPFC) was less deactivated [48]. Similarly, volitional downregulation of drug craving hinges on opposite patterns of activation in the NAc (reduced) versus the dlPFC (increased) [49,50].

The differential influence of DA along striatocortical pathways is partly explained by the subtype of DA receptor being activated. Animal studies indicate that DA receptors have different, albeit complementary, roles in risk-based decision making (for a review see [51]). Specifically, in the mPFC preferential activation of D1 and D2 receptors (D1R and D2R) tips the balance toward or against riskier options, respectively [52]. In the NAc, D1Rs appear to optimize decision making in such a way that their stimulation can increase risky choices (large/uncertain options) when advantageous but shift choice toward small/certain options when their utility declines. By contrast, the stimulation of D3Rs in the NAc appears to decrease the sensitivity to rewards and reduce riskier options, whereas stimulation of D2Rs does not alter choice behaviors associated with risky reward choices [53]. However, D2Rs in the NAc might mediate behavioral choices that result in aversive consequences [54]. Similarly, receptor subtypes mediate reward seeking behaviors: striatal neurons containing predominantly D1Rs promote while those expressing primarily D2Rs inhibit reward-seeking behaviors [55]. Additionally, a subset of neurons expressing D1Rs in the VS (the location of the NAc) are modulated by D3Rs and their activation favors reward seeking [56]. Interestingly, there are D4Rs that modulate the function of D2Rs on the terminals of glutamatergic corticostriatal neurons, and decreased D4R signaling has been implicated in novelty seeking [57,58]. The role of D5Rs in reward has been much less investigated. Finally, impulsivity and sustainability of effort toward a reward have also been shown to be differentially associated with receptor subtype, with distinct modulatory effects in the PFC compared with the NAc [59].

It is likely that the differential impact of various target-area receptor configurations on NOW vs LATER decisions will be predicated on differences in neuronal activation patterns. Although cue-evoked DA bursts in the NAc reflect the value of future rewards, and are clearly involved in reward learning and decision making [60], the DA transients that result from phasic activation of DA neurons are probably not very suitable for the orchestration of behaviors geared toward achieving goals in long time frames. Such calculations are likely to rely on more protracted modes of DA signaling [61,62] that are likely to be more adept at encoding the valence of distant rewards or of sustaining effort. Using fast-scan cyclic voltammetry, a previously unknown, not phasic nor tonic but extendedly

ramping (up or down) mode of DA signaling was recorded in the striatum of rats as they toiled to reach a distant goal that appears particularly well suited to sustaining protracted motivational drive [61]. Perhaps D2Rs, which have high affinity for DA [63] and feature a second, more protracted wave of response during slow synaptic transmission [64], play a more predominant role in this mode of signaling and in orchestrating behaviors to resist the urge for an immediate reward and sustain this resistance as well as maintaining the effort necessary to achieve a long-term goal.

Shifting between NOW vs LATER

The external context and internal state of the individual during the making of NOW vs LATER decisions will modulate proclivity to favor one over the other. The impact of the external context is influenced by prior experience with the stimulus through learned and conditioned responses that rely on brain regions classically associated with memory and expectation (hippocampus, amygdala) and those associated with failed expectation (i.e., the habenula) [65]. Memory of past experience, partly encoded in the hippocampus, allows us to 'imagine' various potential outcomes some time into the future and influences the value that an individual assigns to a simulated option [66]. The amygdala, through its role in processing emotionally laden stimuli [67], also affects impulsivity, DD rates, and goal-directed behaviors [19,68]. Patients with lesions in the basolateral nucleus of the amygdala (BLA) make 'riskier' choices, opting for large rewards NOW even at the expense of significant losses LATER. Additionally, the habenula provides inhibitory tone to DA neurons that project to the NAc when a predicted reward does not materialize or a stimulus is perceived as aversive [69]. Conversely, lateral habenula neurons are inhibited by rewarding stimuli [70], which is likely to remove tonic inhibitory influence on the PFC and NAc [71].

The decision of NOW vs LATER is also influenced by computing the available options on the basis of their intrinsic values, which relies on the orbitofrontal cortex (OFC) and the ACC [72]. The OFC processes salience attribution and is essential for changing the weighted value of a reward as a function of alternative reinforcers and the physiological state of the individual. For example, when starved the salience value of food is much greater than when satiated and this shifting value is conveyed to the NAc through the OFC [73]. Similarly, the OFC will modulate alternative choices to stimuli, such that more rewarding stimuli will be preferred over smaller ones [74] based, among others, on the subjective hedonic value of the reward [75]. Consistent with this role, lesions in the OFC are associated with repetitive behaviors that are not influenced by context or physiological state (i.e., compulsive eating or drug taking) [76]. The ACC plays a central role in error processing and conflict monitoring [77], a contribution that hinges on a form of learning that is driven by outcomes that do not match the prediction [78]. By conveying this conflict-related information to inhibitory circuits, the ACC enables inhibitory learning and facilitates impulse control [79].

Finally, the awareness of the internal state, as it relates to need, desires, or sensations and which relies on the insula [80], also modulates NOW vs LATER decisions. The insula has an overarching role across various modes of self-control, including motor impulsivity as well as reactive aggression [81].

Model of NOW vs LATER circuits

Based on the updated information described above we propose an integrated, albeit simplified model of the complex circuitry that instantiates NOW vs LATER decisions (Figure 1). Computational units within this broad circuit can be generally ascribed to one of three classes depending on whether they facilitate immediate or delayed responses or enable the shifting between them whenever appropriate (coded as green, red, and orange boxes in Figure 1). According to this model, the initial salience of a reward correlates with fast and large elevations of synaptic DA within the NAc [82]. The vmPFC appears to enhance reward salience calculations through its involvement in the processing of the outcome value of that reward. The OFC is critically involved in salience attribution; its main contribution is to offer predictive information about alternative options and outcomes, which is essential for shifting between NOW and LATER rewards. Meanwhile, the ACC enables inhibitory learning by keeping tabs on conflicts between predicted and actual outcomes and conveying that information to executive control/inhibitory circuits orchestrated by the dlPFC and dorsal striatal regions (caudate).

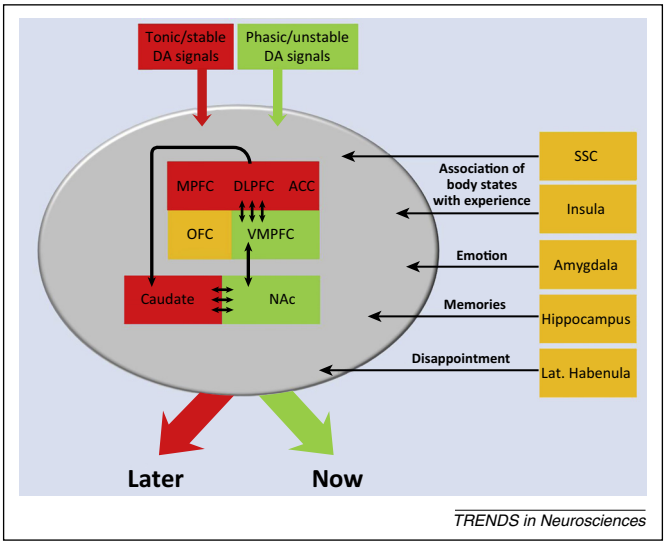

Figure 1. Proposed model of delay discounting (DD) decisions as the result of computations performed within a circuit core that includes cortical [including the dorsolateral prefrontal cortex (dlPFC), medial PFC (mPFC), ventromedial PFC (vmPFC), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC)] and subcortical [including the caudate and nucleus accumbens (NAc) in the dorsal and ventral striatum, respectively] regions. Additional regions and structures modulate DD computations in the core by providing interoceptive information [the somatosensory cortex (SSC) and insula], emotional states (amygdala), reward-associated memories (hippocampus), and input about reward omissions (lateral habenula). Core computations are strongly affected by tonic dopamine (DA) signals that have a strong influence on the dlPFC and favor LATER rewards. Conversely, they are also influenced by phasic DA signaling, which tends to drive the vmPFC/NAc to favor choosing a reward NOW. To ensure optimal choice, these computations are influenced by a broad array of additional, interacting modules that convey critical information about the reward itself, internal states, past experiences, and current conditions, including alternative options and the probability of occurrences. Regions that mediate immediate responses are depicted in green. Regions that mediate delayed responses are depicted in red. Regions that enable a behavioral shift between now and later responses are depicted in orange.

This inhibitory arm of the decision-making process is facilitated in turn by tonic DA signaling sustaining activity in the dlPFC. Together with the insular cortex, which provides key information about the physiological state of the individual, the ACC also allows the circuit to estimate the level of uncertainty involved in choosing among alternative options. Finally, the amygdala, hippocampus, and lateral habenula, which provide information about emotional salience, past experience, and pertinent reward-omission events, respectively, can all contribute to lower DD rates and an ability to shift from NOW to LATER rewards [66,83,84].

Disordered NOW vs LATER processes: addiction and obesity

Repeated exposure to instantly gratifying rewards (like drugs, instant lotteries, or junk food) can trigger or exacerbate preexisting deficits within NOW vs LATER circuits. These disruptions, which can display significant overlaps when probed in disorders such as addiction, gambling, or obesity [85–87], include: (i) decreased signaling through striatal D2Rs (leading to reduced inhibition by DA of the indirect striatocortical pathway), which is associated with reduced activity in frontal regions involved with self-control (dmPFC, dlPFC, and inferior frontal cortex), error monitoring (ACC), and salience attribution (OFC); (ii) increased sensitivity and influence from the amygdala and hippocampus toward stressful stimuli and reward-associated cues; (iii) enhanced interoceptive awareness of desire states that implicate increased activity of the insula and stronger connectivity with the default mode network (DMN), which modulates attention to inner processes; and (iv) increased expectation of reward associated with cues that relate to food (obesity) or to drugs (addiction) with a paradoxical decline in sensitivity to the actual consumption of the reward. This discrepancy between the expected versus the actual experience of consuming the reward is likely to drive the motivation to persist in the NOW behavior until the expected outcome is achieved [22].

The activity of circuits involved with NOW vs LATER processes are likely to be influenced by genetic, developmental, and environmental factors (Box 1), all of which could modulate a person's tendency to make unhealthy choices [3,88] or manifest psychiatric disorders [6,89,90] (right-side arm of Figure 2). There is strong converging evidence to propose DD to be a common core impairment across many disorders characterized by behavioral dyscontrol.

NOW vs LATER circuitry: the linchpin of universal prevention

DD has been suggested to represent a trans-disease process [91], which one could argue reflects an example of 'bow-tie' architecture. This regulatory motif, identifiable in many other complex adaptive systems [92,93], is the result of an evolutionarily optimized organization whereby a narrowing funnel of many potential inputs converges onto one or more master core processes before fanning out again into a great diversity of outputs.

A bow-tie architecture provides an economical and satisfactory heuristic model for conceptualizing NOW vs LATER decisions (Figure 2). It also has clinical implications, for

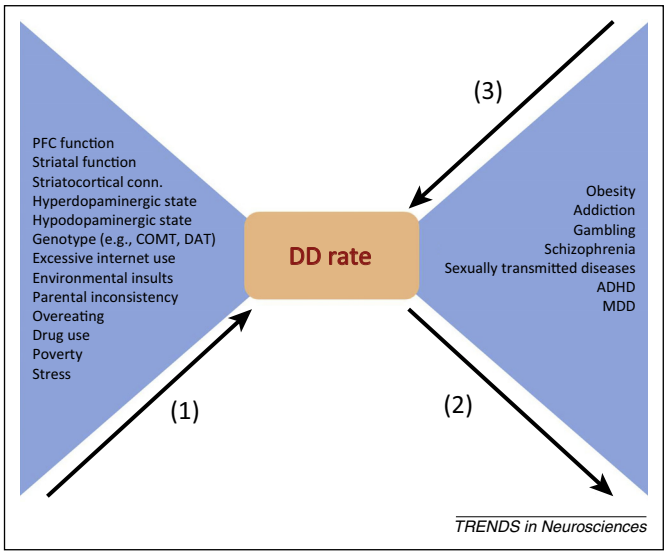

Figure 2. Schematic representation of delay discounting (DD) as another example of bow-tie architecture in the brain. From the input side, DD rates are influenced by a long list of genetic, environmental, developmental, and social factors (arrow 1). On the output side, DD rates can modulate the risk of impulse-control disorders (e.g., obesity, addiction, gambling) as well as a growing number of psychiatric disorders (arrow 2). Importantly, many of the items on the output list have the capacity to feed back and exacerbate the steepness of DD rates (arrow 3) and, thus, clinical prognosis.

it suggests that interventions focused on either protecting or strengthening the ability to delay gratification (improve self-control, reduce DD rates, reduce various components of impulsivity) could help better prevent a wide range of negative behavioral health outcomes. Supporting this is the evidence that early self-control is a robust predictor of long-term physical and behavioral health [94–96]. Moreover, several evidence-based behavioral and/or environmental interventions to strengthen various components of the 'self-control' network could be incorporated into resiliency-building programs [97,98].

NOW vs LATER circuitry: treatment implications

A better understanding of the circuits that underlie NOW vs LATER decisions could lead to significant translational benefits. A recent study, for example, has found that high discounting rates among substance-use disorder (SUD) patients in an inpatient detoxification program were predictive of shorter treatment retention [99]. On the other side of the equation, recent evidence suggests that treatment for anorexia nervosa may help restore normal rates of DD [100]. Moreover, examples of successful manipulation of DD rates for therapeutic purposes are beginning to appear in the scientific literature [101]. This general approach may be especially relevant in light of therapeutic and other technological advances that may allow us to purposefully enhance our ability to access hidden layers of cognition and help counteract operational DD deficits. A wide range of strategies to improve human decision making could hinge on largely subconsciously operating reward-substitution interventions [102], environmental context manipulations [103], and novel brain exercise paradigms like reward training [104], mindful meditation [105], or episodic future thinking, all of which have been shown to enhance PFC control function and thus a person's

ability to generate more future-minded choice behaviors. Other areas ripe for research include better understanding and harnessing of the phenomenon of self-control depletion [106,107] and/or the systematic investigation of how the mere reframing of a reward can enhance self-control without necessarily depleting willpower [108].

The involvement of a dysfunctional insula in DD deficits provides an opportunity to test the hypothesized therapeutic potential of making implicit processes explicit. For example, it has been suggested [109] that a deficit in interoception could be responsible for impaired anticipatory behavior when an environmental situation calls for cognitive flexibility (e.g., when an abstinent cocaine addict is exposed to drug-associated cues). If this is indeed the case, it may be warranted to follow up on the evidence that contemplative practices (e.g., mindfulness) [110] or intense exercise [111] can modulate insular activation patterns and improve interoceptive function [112]. Similar techniques may also be helpful for morbidly obese individuals who may have an impaired ability to tap into such visceral data to more accurately estimate the impact of future negative consequences.

It is worth noting that easing the transfer from implicit to explicit is the hallmark of very different kinds of therapeutic approaches such as neurofeedback [113], 12-step programs [114], cognitive behavioral treatment (CBT) [115,116], and mindfulness training [117]. In the future, we might also be able to complement behavioral or lifestyle change strategies with electric or magnetic stimulation interventions targeting control or interoceptive circuits [118]. For example, repetitive transcranial magnetic stimulation (rTMS) has been successfully used in healthy human volunteers to transiently activate the dmPFC and reduce DD for delayed rewards, an effect that was associated with enhanced DA release in the dorsal striatum whereas there were no DA changes in the NAc [119]. However, these studies have been limited to the evaluation of immediate responses to acute rTMS administration; further studies are required to evaluate the permanence of rTMS-induced changes in DD and in DA release. Also, in the future, access to stimulation devices (magnetic or electrical) that can target specific PFC and ACC regions (or other cortical relevant regions such as the anterior insula) will allow investigators to more precisely modulate neuronal networks through stimulation (high frequency) or inhibition (low frequency) that optimizes behavioral choices. For example, devices that can be used to target more ventral PFC regions and use of rTMS at slow frequencies might result in reduced DA release in the ventral striatum that, when coupled with high-frequency rTMS of the dlPFC, might further reduce impulsive choices.

Concluding remarks: policy implications

Human health and well-being are contingent not only on the state of the NOW vs LATER circuitry but also on that of many other regulatory networks in the brain. Yet, a sharper focus on DD appears justified if we consider not only its potential benefits for universal prevention and behavioral and/or lifestyle interventions (i.e., individual policy) but also its implications *vis-á-vis* public policy.

Box 1. Outstanding questions

- Which genes influence the various components of impulsivity that contribute to DD and what are the mechanisms involved? For example, variants in the COMT gene (Val^{158} allele) have been associated with impulsivity and studies in transgenic mice carrying the human COMT variant have related this to increased DA release [131]. However, it is likely that many other genes make different contributions to distinct components of impulsivity.
- What are the neuronal circuits underlying the various components of impulsivity that contribute to DD (i.e., urgency, lack of perseverance, sensation seeking, and disinhibition)? While much work links impaired function of the PFC with a tendency toward impulsive behaviors and indicates the role of executive control networks in sustaining top-down control as necessary for self-regulation, the details of these interactions are not well understood [132].
- DA is recognized to play a central role in action selection between rewards of different values and probabilities. However, recent findings also show that DA signaling in the NAc correlates with behavioral preferences when the benefits overshadow the costs but not when the costs outweigh the benefits [133]. This suggests the existence of different mechanisms underlying behavioral choices for rewarding options versus those requiring sustained effort.
- What are the policy implications of emerging neurobiological data that clarify how environmental stimuli influence our proclivity toward immediate rewards or how they can facilitate sustained effort?
- What are the ethical considerations that emerge as we learn to manipulate neuronal circuits to optimize certain behaviors that are deemed to be more socially appropriate? What are the consequences for human behavioral diversity?

More specifically, gaining a better understanding of the impact of various environmental factors on NOW vs LATER behavioral choices could be an important priority area for policy research. The Construal Level Theory (CLT) of psychological distance offers an interesting perspective from which to explore this idea.

According to the CLT, as objects move from closer to distant relative to a person, the thinking about that object tends to shift from concrete (low level) to abstract (high level). Thus, it can be argued that a growing number of environmental factors have had the unintended (or intended) effect of promoting low-level while impeding high-level construal. Since this effect is bound to display vast interindividual differences, one way to try to manage the consequences of this shift would be to classify [120] and/or intervene [121] based on an individual's construal of self-control dilemmas. For example, we could envision traits such as neuroticism and conscientiousness being investigated for their validity as construal characterization tools since they have been associated with relatively greater preferences for immediate and delayed rewards, respectively [75].

NOW vs LATER processes are relevant for public health, including the redesigning of policies and environments known to be detrimental to human well-being. For example the widespread availability of highly rewarding and affordable food with high caloric but low nutritional value facilitates inappropriate NOW choices at the expense of adverse health consequences that emerge LATER. Since such foods tend to be much more affordable than healthy foods, those in lower socioeconomic strata are more negatively affected by them. However, this negative impact is

not only influenced by cost, for the mere feeling of being poor negatively affects intertemporal choice [122]. This finding is likely to underlie a host of worrisome public health consequences. For example, overall debt and ratios of debt to income and debt to assets have all been associated with a tendency to forego medical or dental care [123]. Some have even suggested [124] that the exaggerated temporal discounting displayed by individuals with conduct disorder could 'reflect an adaptation to chronic exposure to psychosocial insecurity during development' [125]. Preclinical research even shows that adverse circumstances early in life can perturb the balance between D1Rs and D2Rs in the prelimbic PFC [126] and the expression of plasticity markers in the NAc [127], setting the stage for later problems with NOW (concrete) vs LATER (abstract) decisions [128,129]. Fortunately, our growing knowledge of NOW vs LATER circuitry opens new opportunities for the design of smarter environments that promote healthier behaviors. For example, and taking a cue from the successful marketing strategies that trigger automatic, emotion-based decisions, it should now be possible to design food labels that engage the same implicit mechanisms and nudge us to make better choices [103,130].

Our natural tendency to discount rewards that are less than immediate, harder to achieve, or less likely to materialize should be harnessed to make our world healthier even when it might be costly NOW, for this will be offset by much greater savings from averted health costs LATER.

References

1 Madden, G.J. *et al.* (2009) Pathological gamblers discount probabilistic rewards less steeply than matched controls. *Exp. Clin. Psychopharmacol.* 17, 283–290
2 Nishiyama, R. (2014) Response effort discounts the subjective value of rewards. *Behav. Process.* 107C, 175–177
3 Story, G.W. *et al.* (2014) Does temporal discounting explain unhealthy behavior? A systematic review and reinforcement learning perspective. *Front. Behav. Neurosci.* 8, 76
4 Andrade, L.F. and Petry, N.M. (2012) Delay and probability discounting in pathological gamblers with and without a history of substance use problems. *Psychopharmacology* 219, 491–499
5 Hamilton, K.R. and Potenza, M.N. (2012) Relations among delay discounting, addictions, and money mismanagement: implications and future directions. *Am. J. Drug Alcohol Abuse* 38, 30–42
6 Costa Dias, T.G. *et al.* (2013) Reward circuit connectivity relates to delay discounting in children with attention-deficit/hyperactivity disorder. *Eur. Neuropsychopharmacol.* 23, 33–45
7 Epstein, L.H. *et al.* (2010) Food reinforcement, delay discounting and obesity. *Physiol. Behav.* 100, 438–445
8 MacKillop, J. (2013) Integrating behavioral economics and behavioral genetics: delayed reward discounting as an endophenotype for addictive disorders. *J. Exp. Anal. Behav.* 99, 14–31
9 Reynolds, B. (2006) A review of delay-discounting research with humans: relations to drug use and gambling. *Behav. Pharmacol.* 17, 651–667
10 Takahashi, T. *et al.* (2008) Depressive patients are more impulsive and inconsistent in intertemporal choice behavior for monetary gain and loss than healthy subjects – an analysis based on Tsallis' statistics. *Neuroendocrinol. Lett.* 29, 351–358
11 Bixter, M.T. and Luhmann, C.C. (2013) Adaptive intertemporal preferences in foraging-style environments. *Front. Neurosci.* 7, 93
12 Peters, J. and Buchel, C. (2011) The neural mechanisms of inter-temporal decision-making: understanding variability. *Trends Cogn. Sci.* 15, 227–239
13 Carter, E.C. *et al.* (2015) Reassessing intertemporal choice: human decision-making is more optimal in a foraging task than in a self-control task. *Front. Psychol.* 6, 95
14 Basar, K. *et al.* (2010) Nucleus accumbens and impulsivity. *Prog. Neurobiol.* 92, 533–557
15 Stojek, M.M. *et al.* (2014) The role of impulsivity traits and delayed reward discounting in dysregulated eating and drinking among heavy drinkers. *Appetite* 80, 81–88
16 Whiteside, S.P. and Lynam, D.R. (2001) The Five Factor Model and impulsivity: using a structural model of personality to understand impulsivity. *Pers. Individ. Dif.* 30, 669–689
17 Winstanley, C.A. *et al.* (2006) Double dissociation between serotonergic and dopaminergic modulation of medial prefrontal and orbitofrontal cortex during a test of impulsive choice. *Cereb. Cortex* 16, 106–114
18 Paterson, N.E. *et al.* (2012) Impulsive action and impulsive choice are mediated by distinct neuropharmacological substrates in rat. *Int. J. Neuropsychopharmacol.* 15, 1473–1487
19 Baarendse, P.J. and Vanderschuren, L.J. (2012) Dissociable effects of monoamine reuptake inhibitors on distinct forms of impulsive behavior in rats. *Psychopharmacology* 219, 313–326
20 Floresco, S.B. *et al.* (2008) Dopaminergic and glutamatergic regulation of effort- and delay-based decision making. *Neuropsychopharmacology* 33, 1966–1979
21 Cardinal, R.N. (2006) Neural systems implicated in delayed and probabilistic reinforcement. *Neural Netw.* 19, 1277–1301
22 Volkow, N.D. *et al.* (2014) Stimulant-induced dopamine increases are markedly blunted in active cocaine abusers. *Mol. Psychiatry* 19, 1037–1043
23 Volkow, N.D. *et al.* (2001) Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. *J. Neurosci.* 21, RC121
24 Fowler, J.S. *et al.* (2008) Fast uptake and long-lasting binding of methamphetamine in the human brain: comparison with cocaine. *Neuroimage* 43, 756–763
25 Volkow, N.D. *et al.* (2004) Evidence that methylphenidate enhances the saliency of a mathematical task by increasing dopamine in the human brain. *Am. J. Psychiatry* 161, 1173–1180
26 Ghahremani, D.G. *et al.* (2012) Striatal dopamine D_2/D_3 receptors mediate response inhibition and related activity in frontostriatal neural circuitry in humans. *J. Neurosci.* 32, 7316–7324
27 Robinson, E.S. *et al.* (2009) Behavioural characterisation of high impulsivity on the 5-choice serial reaction time task: specific deficits in 'waiting' versus 'stopping'. *Behav. Brain Res.* 196, 310–316
28 Tricomi, E. *et al.* (2009) A specific role for posterior dorsolateral striatum in human habit learning. *Eur. J. Neurosci.* 29, 2225–2232
29 Coull, J.T. *et al.* (1998) Monitoring for target objects: activation of right frontal and parietal cortices with increasing time on task. *Neuropsychologia* 36, 1325–1334
30 Pardo, J.V. *et al.* (1991) Localization of a human system for sustained attention by positron emission tomography. *Nature* 349, 61–64
31 Jimura, K. *et al.* (2013) Impulsivity and self-control during intertemporal decision making linked to the neural dynamics of reward value representation. *J. Neurosci.* 33, 344–357
32 Mailly, P. *et al.* (2013) The rat prefrontostriatal system analyzed in 3D: evidence for multiple interacting functional units. *J. Neurosci.* 33, 5718–5727
33 Brooks, A.M. and Berns, G.S. (2013) Aversive stimuli and loss in the mesocorticolimbic dopamine system. *Trends Cogn. Sci.* 17, 281–286
34 Wager, T.D. *et al.* (2004) Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science* 303, 1162–1167
35 Essex, B.G. *et al.* (2012) The impact of the posterior parietal and dorsolateral prefrontal cortices on the optimization of long-term versus immediate value. *J. Neurosci.* 32, 15403–15413
36 McClure, S.M. *et al.* (2004) Separate neural systems value immediate and delayed monetary rewards. *Science* 306, 503–507
37 Sellitto, M. *et al.* (2011) The neurobiology of intertemporal choice: insight from imaging and lesion studies. *Rev. Neurosci.* 22, 565–574
38 Seymour, B. *et al.* (2004) Temporal difference models describe higher-order learning in humans. *Nature* 429, 664–667
39 Kable, J.W. and Glimcher, P.W. (2010) An "as soon as possible" effect in human intertemporal decision making: behavioral evidence and neural mechanisms. *J. Neurophysiol.* 103, 2513–2531
40 Bermudez, M.A. and Schultz, W. (2014) Timing in reward and decision processes. *Philos. Trans. R. Soc. Lond. B: Biol. Sci.* 369, 20120468

41 Abler, B. *et al.* (2006) Prediction error as a linear function of reward probability is coded in human nucleus accumbens. *Neuroimage* 31, 790–795
42 Spicer, J. *et al.* (2007) Sensitivity of the nucleus accumbens to violations in expectation of reward. *Neuroimage* 34, 455–461
43 Kalivas, P.W. *et al.* (1993) GABA and enkephalin projection from the nucleus accumbens and ventral pallidum to the ventral tegmental area. *Neuroscience* 57, 1047–1060
44 Schultz, W. (2007) Behavioral dopamine signals. *Trends Neurosci.* 30, 203–210
45 Wise, R.A. (2002) Brain reward circuitry: insights from unsensed incentives. *Neuron* 36, 229–240
46 St Onge, J.R. *et al.* (2012) Dynamic fluctuations in dopamine efflux in the prefrontal cortex and nucleus accumbens during risk-based decision making. *J. Neurosci.* 32, 16880–16891
47 Boettiger, C.A. *et al.* (2007) Immediate reward bias in humans: fronto-parietal networks and a role for the catechol-*O*-methyltransferase $158^{Val/Val}$ genotype. *J. Neurosci.* 27, 14383–14391
48 Stanger, C. *et al.* (2013) Neuroeconomics and adolescent substance abuse: individual differences in neural networks and delay discounting. *J. Am. Acad. Child Adolesc. Psychiatry* 52, 747–755
49 Kober, H. *et al.* (2010) Prefrontal–striatal pathway underlies cognitive regulation of craving. *Proc. Natl. Acad. Sci. U.S.A.* 107, 14811–14816
50 Volkow, N.D. *et al.* (2010) Cognitive control of drug craving inhibits brain reward regions in cocaine abusers. *Neuroimage* 49, 2536–2543
51 Floresco, S.B. and Magyar, O. (2006) Mesocortical dopamine modulation of executive functions: beyond working memory. *Psychopharmacology* 188, 567–585
52 St Onge, J.R. *et al.* (2011) Dissociable contributions by prefrontal D1 and D2 receptors to risk-based decision making. *J. Neurosci.* 31, 8625–8633
53 Stopper, C.M. *et al.* (2013) Receptor-specific modulation of risk-based decision making by nucleus accumbens dopamine. *Neuropsychopharmacology* 38, 715–728
54 Stopper, C.M. and Floresco, S.B. (2015) Dopaminergic circuitry and risk/reward decision making: implications for schizophrenia. *Schizophr. Bull.* 41, 9–14
55 Maia, T.V. and Frank, M.J. (2011) From reinforcement learning models to psychiatric and neurological disorders. *Nat. Neurosci.* 14, 154–162
56 Fiorentini, C. *et al.* (2010) Dimerization of dopamine D1 and D3 receptors in the regulation of striatal function. *Curr. Opin. Pharmacol.* 10, 87–92
57 Reist, C. *et al.* (2007) Novelty seeking and the dopamine D4 receptor gene (DRD4) revisited in Asians: haplotype characterization and relevance of the 2-repeat allele. *Am. J. Med. Genet. B: Neuropsychiatr. Genet.* 144B, 453–457
58 Tsuchimine, S. *et al.* (2009) Minor genetic variants of the dopamine D4 receptor (DRD4) polymorphism are associated with novelty seeking in healthy Japanese subjects. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 33, 1232–1235
59 Simon, N.W. *et al.* (2013) Prefrontal cortical–striatal dopamine receptor mRNA expression predicts distinct forms of impulsivity. *Eur. J. Neurosci.* 37, 1779–1788
60 Day, J.J. *et al.* (2010) Phasic nucleus accumbens dopamine release encodes effort- and delay-related costs. *Biol. Psychiatry* 68, 306–309
61 Howe, M.W. *et al.* (2013) Prolonged dopamine signalling in striatum signals proximity and value of distant rewards. *Nature* 500, 575–579
62 Niv, Y. *et al.* (2007) Tonic dopamine: opportunity costs and the control of response vigor. *Psychopharmacology* 191, 507–520
63 Missale, C. *et al.* (1998) Dopamine receptors: from structure to function. *Physiol. Rev.* 78, 189–225
64 Beaulieu, J.M. and Gainetdinov, R.R. (2011) The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacol. Rev.* 63, 182–217
65 Bromberg-Martin, E.S. and Hikosaka, O. (2011) Lateral habenula neurons signal errors in the prediction of reward information. *Nat. Neurosci.* 14, 1209–1216
66 Lebreton, M. *et al.* (2013) A critical role for the hippocampus in the valuation of imagined outcomes. *PLoS Biol.* 11, e1001684
67 LeDoux, J. (2007) The amygdala. *Curr. Biol.* 17, R868–R874
68 Gallagher, M. (2000) The amygdala and associative learning. In *The Amygdala: A Functional Analysis* (Aggleton, J.P., ed.), pp. 311–329, Oxford University Press
69 Velasquez, K.M. *et al.* (2014) The role of the habenula in drug addiction. *Front. Hum. Neurosci.* 8, 174
70 Matsumoto, M. and Hikosaka, O. (2007) Lateral habenula as a source of negative reward signals in dopamine neurons. *Nature* 447, 1111–1115
71 Lecourtier, L. *et al.* (2008) Differential tonic influence of lateral habenula on prefrontal cortex and nucleus accumbens dopamine release. *Eur. J. Neurosci.* 27, 1755–1762
72 Rolls, E.T. (2013) A biased activation theory of the cognitive and attentional modulation of emotion. *Front. Hum. Neurosci.* 7, 74
73 Stice, E. *et al.* (2009) Relation of obesity to consummatory and anticipatory food reward. *Physiol. Behav.* 97, 551–560
74 Kahnt, T. *et al.* (2010) The neural code of reward anticipation in human orbitofrontal cortex. *Proc. Natl. Acad. Sci. U.S.A.* 107, 6010–6015
75 Peters, J. and Buchel, C. (2010) Neural representations of subjective reward value. *Behav. Brain Res.* 213, 135–141
76 Volkow, N.D. and Fowler, J.S. (2000) Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. *Cereb. Cortex* 10, 318–325
77 van Veen, V. and Carter, C.S. (2002) The anterior cingulate as a conflict monitor: fMRI and ERP studies. *Physiol. Behav.* 77, 477–482
78 Klavir, O. *et al.* (2013) Functional connectivity between amygdala and cingulate cortex for adaptive aversive learning. *Neuron* 80, 1290–1300
79 Holroyd, C.B. and Coles, M.G. (2002) The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. *Psychol. Rev.* 109, 679–709
80 Wiebking, C. *et al.* (2014) GABA in the insula – a predictor of the neural response to interoceptive awareness. *Neuroimage* 86, 10–18
81 Dambacher, F. *et al.* (2014) Out of control: evidence for anterior insula involvement in motor impulsivity and reactive aggression. *Soc. Cogn. Affect. Neurosci.* 10, 508–516
82 Volkow, N.D. *et al.* (2009) Imaging dopamine's role in drug abuse and addiction. *Neuropharmacology* 56 (Suppl. 1), 3–8
83 Winstanley, C.A. *et al.* (2004) Contrasting roles of basolateral amygdala and orbitofrontal cortex in impulsive choice. *J. Neurosci.* 24, 4718–4722
84 Kobayashi, Y. *et al.* (2013) Genetic dissection of medial habenula–interpeduncular nucleus pathway function in mice. *Front. Behav. Neurosci.* 7, 17
85 Goudriaan, A.E. *et al.* (2014) Getting a grip on problem gambling: what can neuroscience tell us? *Front. Behav. Neurosci.* 8, 141
86 Tomasi, D. and Volkow, N.D. (2013) Striatocortical pathway dysfunction in addiction and obesity: differences and similarities. *Crit. Rev. Biochem. Mol. Biol.* 48, 1–19
87 van Holst, R.J. *et al.* (2014) Striatal connectivity changes following gambling wins and near-misses: associations with gambling severity. *Neuroimage Clin.* 5, 232–239
88 Irvine, M.A. *et al.* (2013) Impaired decisional impulsivity in pathological videogamers. *PLoS ONE* 8, e75914
89 Pulcu, E. *et al.* (2014) Temporal discounting in major depressive disorder. *Psychol. Med.* 44, 1825–1834
90 Ahn, W.Y. *et al.* (2011) Temporal discounting of rewards in patients with bipolar disorder and schizophrenia. *J. Abnorm. Psychol.* 120, 911–921
91 Bickel, W.K. *et al.* (2012) Excessive discounting of delayed reinforcers as a trans-disease process contributing to addiction and other disease-related vulnerabilities: emerging evidence. *Pharmacol. Ther.* 134, 287–297
92 Csete, M. and Doyle, J. (2004) Bow ties, metabolism and disease. *Trends Biotechnol.* 22, 446–450
93 Volkow, N.D. *et al.* (2013) The addictive dimensionality of obesity. *Biol. Psychiatry* 73, 811–818
94 Fergusson, D.M. *et al.* (2013) Childhood self-control and adult outcomes: results from a 30-year longitudinal study. *J. Am. Acad. Child Adolesc. Psychiatry* 52, 709–717
95 Moffitt, T.E. *et al.* (2011) A gradient of childhood self-control predicts health, wealth, and public safety. *Proc. Natl. Acad. Sci. U.S.A.* 108, 2693–2698
96 Mischel, W. *et al.* (2011) 'Willpower' over the life span: decomposing self-regulation. *Soc. Cogn. Affect. Neurosci.* 6, 252–256

97 Greenberg, M.T. (2006) Promoting resilience in children and youth: preventive interventions and their interface with neuroscience. *Ann. N. Y. Acad. Sci.* 1094, 139–150
98 Rutter, M. (2013) Annual research review: resilience – clinical implications. *J. Child Psychol. Psychiatry* 54, 474–487
99 Stevens, L. *et al.* (2015) Delay discounting, treatment motivation and treatment retention among substance-dependent individuals attending an in inpatient detoxification program. *J. Subst. Abuse Treat.* 49, 58–64
100 Decker, J.H. *et al.* (2014) On weight and waiting: delay discounting in anorexia nervosa pretreatment and posttreatment. *Biol. Psychiatry* Published online December 23, 2014. http://dx.doi.org/10.1016/j.biopsych.2014.12.016
101 Koffarnus, M.N. *et al.* (2013) Changing delay discounting in the light of the competing neurobehavioral decision systems theory: a review. *J. Exp. Anal. Behav.* 99, 32–57
102 Darlington, T.M. *et al.* (2014) Mesolimbic transcriptional response to hedonic substitution of voluntary exercise and voluntary ethanol consumption. *Behav. Brain Res.* 259, 313–320
103 Wansink, B. *et al.* (2012) Attractive names sustain increased vegetable intake in schools. *Prev. Med.* 55, 330–332
104 Schonberg, T. *et al.* (2014) Influencing food choices by training: evidence for modulation of frontoparietal control signals. *J. Cogn. Neurosci.* 26, 247–268
105 Tang, Y.Y. and Posner, M.I. (2014) Training brain networks and states. *Trends Cogn. Sci.* 18, 345–350
106 Baumeister, R.F. (2014) Self-regulation, ego depletion, and inhibition. *Neuropsychologia* 65, 313–319
107 Dang, J. *et al.* (2014) Self-control depletion is more than motivational switch from work to fun: the indispensable role of cognitive adaptation. *Front. Psychol.* 5, 933
108 Magen, E. *et al.* (2014) Behavioral and neural correlates of increased self-control in the absence of increased willpower. *Proc. Natl. Acad. Sci. U.S.A.* 111, 9786–9791
109 Paulus, M.P. *et al.* (2009) The role of interoception and alliesthesia in addiction. *Pharmacol. Biochem. Behav.* 94, 1–7
110 Dickenson, J. *et al.* (2013) Neural correlates of focused attention during a brief mindfulness induction. *Soc. Cogn. Affect. Neurosci.* 8, 40–47
111 Williamson, J.W. *et al.* (1999) Activation of the insular cortex is affected by the intensity of exercise. *J. Appl. Physiol.* 87, 1213–1219
112 Paulus, M.P. *et al.* (2013) Treatment approaches for interoceptive dysfunctions in drug addiction. *Front. Psychiatry* 4, 137
113 Hanlon, C.A. *et al.* (2013) Reduction of cue-induced craving through realtime neurofeedback in nicotine users: the role of region of interest selection and multiple visits. *Psychiatry Res.* 213, 79–81
114 Steigerwald, F. and Stone, D. (1999) Cognitive restructuring and the 12-step program of alcoholics anonymous. *J. Subst. Abuse Treat.* 16, 321–327
115 Maas, J. *et al.* (2013) Changing automatic behavior through self-monitoring: does overt change also imply implicit change? *J. Behav. Ther. Exp. Psychiatry* 44, 279–284
116 Ritter, V. *et al.* (2013) Changes in implicit and explicit self-esteem following cognitive and psychodynamic therapy in social anxiety disorder. *Psychother. Res.* 23, 547–558
117 Haase, L. *et al.* (2014) Mindfulness-based training attenuates insula response to an aversive interoceptive challenge. *Soc. Cogn. Affect. Neurosci.* Published online April 8, 2014. http://dx.doi.org/10.1093/scan/nsu042
118 Fecteau, S. *et al.* (2007) Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. *J. Neurosci.* 27, 12500–12505
119 Cho, S.S. *et al.* (2014) Investing in the future: stimulation of the medial prefrontal cortex reduces discounting of delayed rewards. *Neuropsychopharmacology* 40, 546–553
120 Fujita, K. and Carnevale, J. (2012) Transcending temptation through abstraction: the role of construal level in self control. *Curr. Dir. Psychol. Sci.* 21, 248–252
121 Chiou, W.B. *et al.* (2013) Think abstractly, smoke less: a brief construal-level intervention can promote self-control, leading to reduced cigarette consumption among current smokers. *Addiction* 108, 985–992
122 Liu, L. *et al.* (2012) Adapting to the destitute situations: poverty cues lead to short-term choice. *PLoS ONE* 7, e33950
123 Kalousova, L. and Burgard, S.A. (2013) Debt and foregone medical care. *J. Health Soc. Behav.* 54, 204–220
124 Sonuga-Barke, E.J. (2014) Reward: commentary. Temporal discounting in conduct disorder: toward an experience-adaptation hypothesis of the role of psychosocial insecurity. *J. Pers. Disord.* 28, 19–24
125 White, S.F. *et al.* (2014) Reward: empirical contribution. Temporal discounting and conduct disorder in adolescents. *J. Pers. Disord.* 28, 5–18
126 Brenhouse, H.C. *et al.* (2013) Early life adversity alters the developmental profiles of addiction-related prefrontal cortex circuitry. *Brain Sci.* 3, 143–158
127 Burton, C.L. *et al.* (2007) Prenatal restraint stress and motherless rearing disrupts expression of plasticity markers and stress-induced corticosterone release in adult female Sprague–Dawley rats. *Brain Res.* 1158, 28–38
128 Liberman, N. and Trope, Y. (2008) The psychology of transcending the here and now. *Science* 322, 1201–1205
129 Ronteltap, A. *et al.* (2012) Construal levels of healthy eating. Exploring consumers' interpretation of health in the food context. *Appetite* 59, 333–340
130 Grabenhorst, F. *et al.* (2013) Food labels promote healthy choices by a decision bias in the amygdala. *Neuroimage* 74, 152–163
131 Simpson, E.H. *et al.* (2014) Genetic variation in COMT activity impacts learning and dopamine release capacity in the striatum. *Learn. Mem.* 21, 205–214
132 Sebastian, A. *et al.* (2014) Frontal dysfunctions of impulse control – a systematic review in borderline personality disorder and attention-deficit/hyperactivity disorder. *Front. Hum. Neurosci.* 8, 698
133 Hollon, N.G. *et al.* (2014) Dopamine-associated cached values are not sufficient as the basis for action selection. *Proc. Natl. Acad. Sci. U.S.A.* 111, 18357–18362